IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, ADRIAN PAUL BROWN, M.A., M.I.L., M.I.T.I., declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 5 Gilbert Road, London, SE11 4NZ.

2. That I am well acquainted with the French and English languages.

3. That the attached is a true translation into the English language of the certified copy of French Patent Application No. 02 04222 filed on 5 April 2002.

4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 21st DAY OF JULY 2004

A. P. Brown

A P BROWN

FRENCH REPUBLIC

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PATENT OF INVENTION

UTILITY CERTIFICATE - CERTIFICATE OF ADDITION

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Issued in Paris, 23 APR. 2004

For the Director General of the
National Institute for Industrial Property,
The Head of the Patents Department

(signature)

Martine PLANCHE

HEAD OFFICE

NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

26 bis, rue de Saint-Petersbourg
75800 PARIS cedex 08
Telephone: 33 (0)1 53 04 53 04
Facsimile: 33 (0)1 53 04 45 23
www.inpi.fr

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National Institute for Industrial Property
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 94 86 54

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No. 11354*01

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Your references for this file *(optional)* 18886-ASP	

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2 NATURE OF THE APPLICATION	**Mark one of the following 4 boxes**
Patent application	☒
Application for a Utility Certificate	☐
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or initial utility certificate application	No. Date
Conversion of a European Patent Application	☐
Initial patent application	No. Date

3 TITLE OF THE INVENTION (maximum 200 characters or spaces)
NEW ASSOCIATION OF AN ANTITHROMBOTIC AND ASPIRIN.

4 DECLARATION OF PRIORITY OR REQUEST FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION	Country or organisation Date No. Country or organisation Date No. Country or organisation Date No. ☐ **If there are other priorities, mark the box and use the "Continuation" form**
5 APPLICANT	☐ **If there are other Applicants, mark the box and use the "Continuation" form**
Surname or company name	LES LABORATOIRES SERVIER
Forenames	
Legal nature	
SIREN No.	
APE-NAF Code	
Address — Street	1, rue Carle Hébert
Address — Postal code and town	92415 COURBEVOIE cedex
Country	FRANCE
Nationality	FRENCH
Telephone no. *(optional)*	01.55.72.60.00
Facsimile no. *(optional)*	01.55.72.72.13
E-mail address *(optional)*	

First filing

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PATENT OF INVENTION
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DEPOSITION OF DOCUMENTS DATE **5 APRIL 2002** PLACE **75 INPI PARIS** NATIONAL REGISTRATION NO. GIVEN BY THE INPI **0204222**

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6 AUTHORISED AGENT		
Surname		JAGUELIN-GUINAMANT
Forename		Sylvie
Practice or company		LES LABORATOIRES SERVIER
No. of standing power of attorney and/or of contractual bond		
Address	Street	1, rue Carle Hébert
	Postal code and town	92415 COURBEVOIE Cedex (France)
Telephone no. *(optional)*		01.55.72.68.07
Facsimile no. *(optional)*		01.55.72.72.13
E-mail address *(optional)*		
7 INVENTOR(S)		
The inventors are the Applicants		☐ Yes ☒ No **In this case, supply a separate designation of inventorship**
8 SEARCH REPORT		**For a patent application only (including division and conversion)**
immediate drawing up or deferred drawing up		☒ ☐
Payment of the fees in instalments		**Payment in three instalments, for natural persons only** ☐ Yes ☐ No
9 REDUCTION IN FEES		**For natural persons only** ☐ Requested for the first time for this invention *(attach a notice of non-imposition)* ☐ Requested prior to this deposit *(attach a copy of the admissibility decision for this invention or indicate its reference)*
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10 SIGNATURE OF THE APPLICANT OR OF THE AUTHORISED AGENT **(Name and position of signatory)**	**STAMP OF THE PREFECTURE OR OF THE INPI**
(signature) S. JAGUELIN-GUINAMANT, Patent Engineer	[signature] L. GUICHET

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The new invention relates to a new association of an antithrombotic and aspirin and to pharmaceutical compositions containing them.

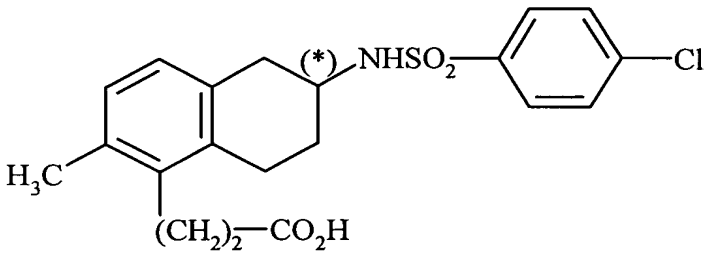
More specifically, the present invention relates to the association of a TP receptor antagonist and aspirin.

Thromboxane A_2 (TXA_2) is an unstable metabolite of arachidonic acid which is involved in the pathogenesis of numerous disorders of blood circulation. Thromboxane A_2 is a powerful platelet activator but is also a powerful vasoconstrictor which has cell proliferative and pro-adhesive properties.

TXA_2 and other metabolites of arachidonic acid such as endoperoxide (PGH_2), HETEs and isoprostanes exert their action by way of common receptors called TP receptors.

Numerous research studies have recently been carried out with the aim of preventing circulatory disorders caused by the excessive production of thromboxane A_2. Among such antagonists, those described in the Patent Specification EP 648 741 have been found to be powerful and selective antagonists of TP receptors, to be active *via* the oral route and to have a long duration of action.

More specifically, the compound (A) of formula (I) :



(I),

in racemic form or in the form of an optically pure isomer, and also pharmaceutically acceptable salts thereof, has been found to be a powerful antithrombotic.

That compound selectively inhibits blood platelet aggregation caused by activation of the TP receptors and, moreover, has anti-atherosclerotic properties after administration by the oral route.

We have now found that the association of compound A and aspirin allows, surprisingly, a synergy to be obtained in terms of antithrombotic activity.

It has been described in the literature that certain associations of anti-platelet aggregation agents such as dipyridamole and aspirin have additive effects and that such an association has been shown to be of value in the prevention of cerebral vascular accidents.

Other associations of anti-platelet aggregation agents with aspirin have been described in the literature. In view of the fact that those anti-aggregation agents act on platelet aggregation pathways (such as the purinergic pathways, ADP) which are different from those of aspirin, which acts via the pathway of arachidonic acid metabolism, it was expected that additive effects on the activity of those compounds would be observed.

The association to which the present invention relates is, for its part, completely different: compound A and aspirin both act on the arachidonic acid metabolism pathways: the former acts by irreversibly inhibiting the cyclo-oxygenases, which convert arachidonic acid into endoperoxide (PGH_2) and the latter acts by opposing the activity of certain metabolites of arachidonic acid such as thromboxane A_2, the isoprostanes and endoperoxide.

It has been found, surprisingly, that the association of compound A and aspirin allows substantial synergy to be obtained in terms of activity, which could not have been foreseen from any teaching of the literature.

That synergistic effect has been demonstrated in an arterial thrombosis test in the guinea-pig. In the course of that test it was shown that the antithrombotic activity of compound A is potentiated in the presence of aspirin and increases in extremely substantial and entirely unforeseeable manner.

In the associations according to the invention, compound (A) and aspirin can be present in the form of pharmaceutically acceptable salts.

Among the addition salts of compound (A), there may be mentioned, without implying any limitation, addition salts with a pharmaceutically acceptable base, such as sodium, potassium, *tert*-butylamine and diethylamine salts etc..

Preference will be given to use of the sodium salt.

Among the addition salts of aspirin, there may be mentioned, without implying any limitation, addition salts with a pharmaceutically acceptable acid, such as acetate, benzoate, fumarate, maleate, citrate, tartrate, the lysine salt etc..

In the associations according to the invention, compound (A) preferably has the absolute configuration (R).

The present invention relates also to pharmaceutical compositions comprising an association of compound (A) and aspirin, where appropriate in the form of pharmaceutically acceptable salts, together with one or more appropriate, inert, non-toxic excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels etc..

The dosage can be varied according to the nature and severity of the condition, the administration route and also the age and weight of the patient.

In the compositions according to the invention, the amounts of active ingredients are in the range from 1 to 300 mg for compound (A) and from 100 to 1000 mg for aspirin.

The compositions according to the invention are accordingly useful in the treatment of atherothrombotic illnesses involving the activation of TP receptors and/or the formation of metabolites and also in the treatment of consequences of those illnesses. Those pathologies

include, without implying any limitation, stable or unstable angina, endothelial or vascular dysfunction accompanying illnesses such as hypertension, diabetes, heart failure, disorders of the cardiovascular or cerebrovascular system, or thrombo-embolic disorders associated especially with atherosclerosis.

The associations according to the invention have been studied and the synergy effect has been demonstrated in an arterial thrombosis test in the guinea-pig.

This test is based on the model initially described by Roux *et al.* (Thromb Haemost 71 : 252-256, 1994). The guinea-pigs are anaesthetised using ketamine + xylazine (90 + 12) mg.kg i.m.. The trachea is cannulated and spontaneous respiration by the animals maintained. The jugular vein is cannulated, allowing the intravenous administration of the compounds being tested. The carotid artery is isolated, and a Doppler probe is installed allowing the arterial blood flow to be measured. After stabilisation, a lesion to the artery wall is produced by means of a clip applied distally to the Doppler probe. Subsequent to that lesion, the blood flow decreases. When the flow reaches zero, the artery is lightly shaken, which allows the flow to be restored. The thrombosis process continues, leading again to the flow reducing and ceasing. The thrombotic phenomena accordingly result in cyclic flow reductions (CFR), which are observed over a period of 20 minutes. After that period, the animal is treated, or not, with compound (A), and the CFR are again observed for a period of 20 minutes. The experiments are carried out in control animals or in animals treated by the intravenous route with aspirin (2 mg/kg).

This study was carried out using the sodium salt of the (R) isomer of compound (A).

The results show that 10 ± 1 CFR/20 min are observed in the untreated animals. Compound (A), administered by the intravenous route, reduces the CFR in dose-dependent manner; a significant effect is obtained from the 0.3 mg/kg dose (5 ± 2 CFR/20 min). Almost total inhibition (2 ± 2 CFR/20 min) is obtained with a dose of 1 mg/kg.

In the animals treated with aspirin, 8 ± 1 CFR/20 min are observed; that value is not different from that obtained in the control animals.

Compound (A), administered by the intravenous route to animals already treated with aspirin, reduces the CFR in dose-dependant manner; a significant effect is now obtained

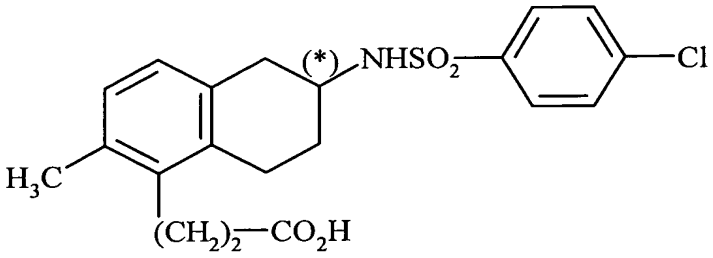
from the 0.01 mg/kg dose (5 ± 1 CFR/20 min), and almost complete inhibition is obtained with a dose of 0.1 mg/kg (2 ± 1 CFR/20 min).

Those results firstly show the powerful antithrombotic activity of compound (A), which is active from the 0.3 mg/kg dose.

Moreover, in the presence of a dose of aspirin which does not bring about an antithrombotic effect, the antithrombotic activity of compound (A) is potentiated and increased by at least 30 times. In fact, that effect is observed from the 0.01 mg/kg dose, which means that there exists a very substantial synergy effect when the two active ingredients are administered simultaneously.

CLAIMS

1- Association of compound (A) of formula (I), optionally in the form of an optical isomer or one of its pharmaceutically acceptable salts, and aspirin, or one of its pharmaceutically acceptable salts :



(I).

2- Association according to claim 1, characterised in that compound (A) is in (R) configuration optical isomer form.

3- Association according to either claim 1 or claim 2, characterised in that compound (A) is in the form of a sodium salt.

4- Pharmaceutical composition comprising as active ingredients an association of compound (A), optionally in the form of an optical isomer or one of its pharmaceutically acceptable salts, and aspirin, or one of its pharmaceutically acceptable salts, in combination with one or more pharmaceutically acceptable, inert excipients or carriers.

5- Pharmaceutical composition according to claim 4, characterised in that compound (A) is in (R) configuration optical isomer form.

6- Pharmaceutical composition according to either claim 4 or claim 5, characterised in that compound (A) is in sodium salt form.

7- Pharmaceutical composition according to any one of claims 4 to 6, characterised in that the amounts of active ingredients are in the respective ranges of from 1 to 300 mg for compound (A) and from 10 to 1000 mg for aspirin.

8- Pharmaceutical composition according to any one of claims 4 to 7, for use in the treatment of atherothrombotic illnesses involving the activation of TP receptors and/or the formation of metabolites and also in the treatment of consequences of those illnesses.

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PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30

PATENT OF INVENTION *cerfa*
UTILITY CERTIFICATE No. 11235*02
Intellectual Property Code - Book VI

DECLARATION OF INVENTORSHIP

(if the applicant is not the inventor or not the only inventor)

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NATIONAL REGISTRATION NO.		0204222	
TITLE OF THE INVENTION (maximum 200 characters or spaces) NEW ASSOCIATION OF AN ANTITHROMBOTIC AND ASPIRIN.			
APPLICANT(S): LES LABORATOIRES SERVIER 1, rue Carle Hébert 92415 COURBEVOIE Cedex FRANCE			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Surname		VERBEUREN	
Forenames		Tony	
Address	Street	60 bis, rue Aristide Briand	
	Postal code and town	78540	VERNOUILLET (France)
Belonging company *(optional)*			
Surname		LAVIELLE	
Forenames		Gilbert	
Address	Street	1, avenue Lily	
	Postal code and town	78170	LA CELLE SAINT CLOUD (France)
Belonging company *(optional)*			
Surname		CIMETIERE	
Forenames		Bernard	
Address	Street	37, cours de Vincennes	
	Postal code and town	75020	PARIS (France)
Belonging company *(optional)*			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) 5th April 2002 (signature) S. JAGUELIN-GUINAMANT, Patent Engineer			

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cerfa
No. 11235*02

PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30

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DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Surname		VALLEZ	
Forenames		Marie-Odile	
Address	Street	4, allée des Charmilles	
	Postal code and town	77420	CHAMPS SUR MARNE (France)
Belonging company *(optional)*			
Surname			
Forenames			
Address	Street		
	Postal code and town		
Belonging company *(optional)*			
Surname			
Forenames			
Address	Street		
	Postal code and town		
Belonging company *(optional)*			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) 5th April 2002 (signature) S. JAGUELIN-GUINAMANT, Patent Engineer			

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